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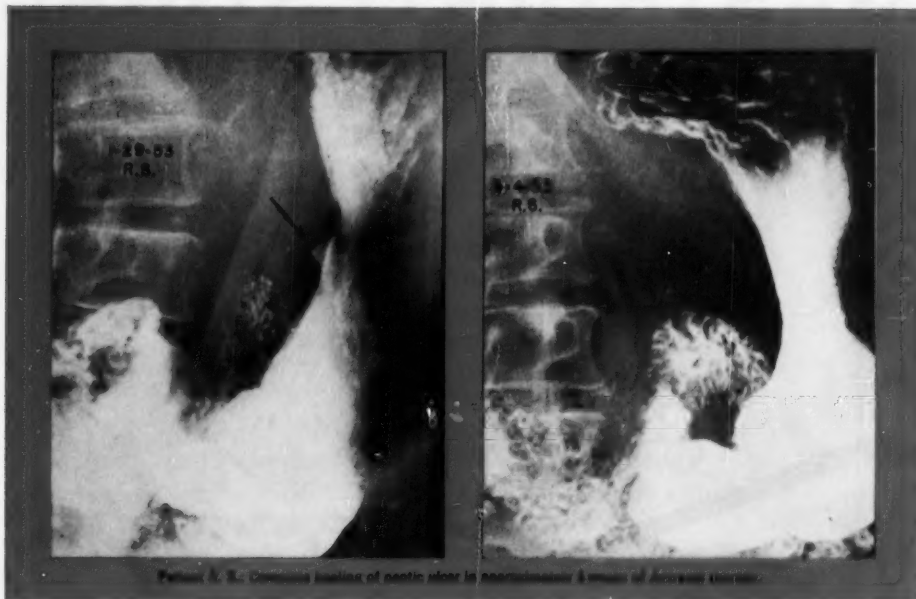
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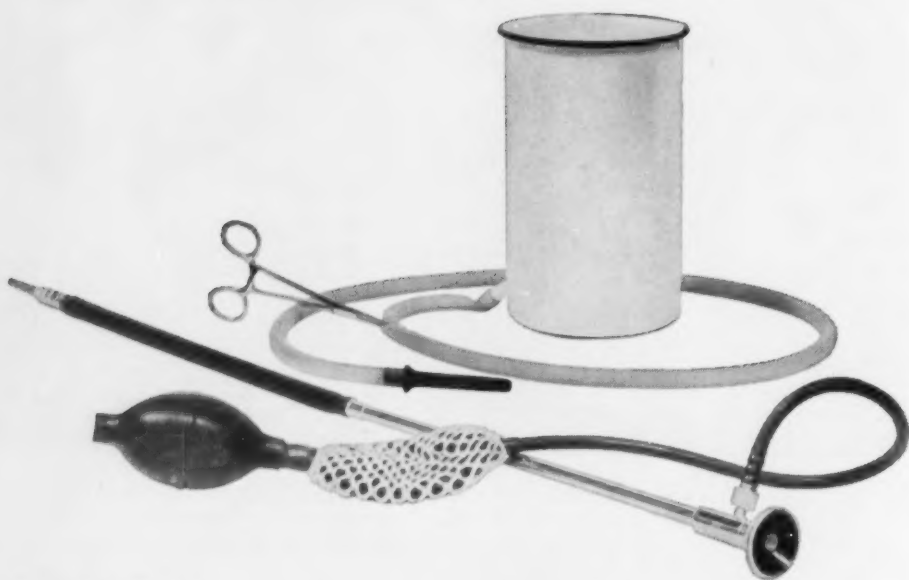
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- ORAL MELANIN PIGMENTATION IN INTESTINAL POLY-
POSIS: HISTOPATHOLOGIC CONSIDERATIONS
*Edward V. Zegarelli, D.D.S., Austin
H. Kutscher, D.D.S., John D. Piro,
D.D.S., and Norman Kupferberg, B.A.* 455
- CHOLOGRAFIN METHYLGLUCAMINE: NEW CONTRAST
MEDIUM FOR INTRAVENOUS CHOLANGIOGRAPHY
AND CHOLECYSTOGRAPHY
*William H. Shehadi, M.D., and Issa
Sabbag, M.D.* 466
- ANNULAR PANCREAS: ROENTGEN MANIFESTATIONS
*Maxwell H. Poppel, M.D., and Samuel
L. Beranbaum, M.D.* 476
- CASE REPORT: PSEUDOMEMBRANOUS ENTEROCOLITIS
DUE TO STAPHYLOCOCCAL INFECTION AND IN-
TESTINAL OBSTRUCTION
Victor W. Groisser, M.D. 484
- EDITORIAL: SPRUE IN PUERTO RICO
*William H. Crosby, Lt. Col., MC,
U. S. Army* 493
- PEARLS OF GASTROENTEROLOGY
Eddy D. Palmer, M.D. 497

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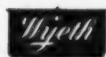
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1. Ralli, E. P., and Dumm, M. E.: The Hormonal Control of Metabolism, in Wohl, M. G.: *Modern Nutrition in Health and Disease*, Philadelphia, Lea and Febiger, 1955, pp. 57-74.
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5. Samuels, L. T.: *Progress in Clinical Endocrinology*, New York, Grune and Stratton, 1950, p. 509.

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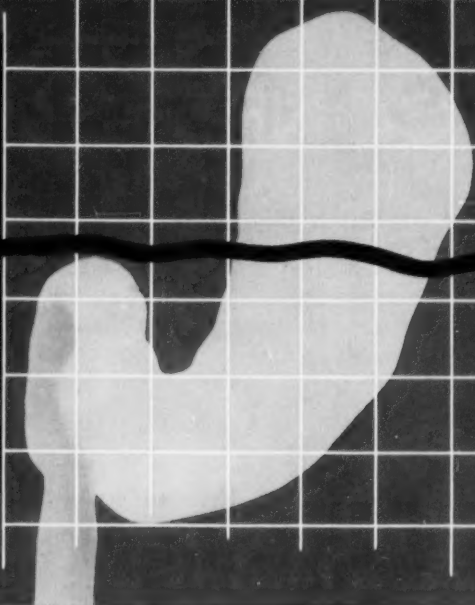
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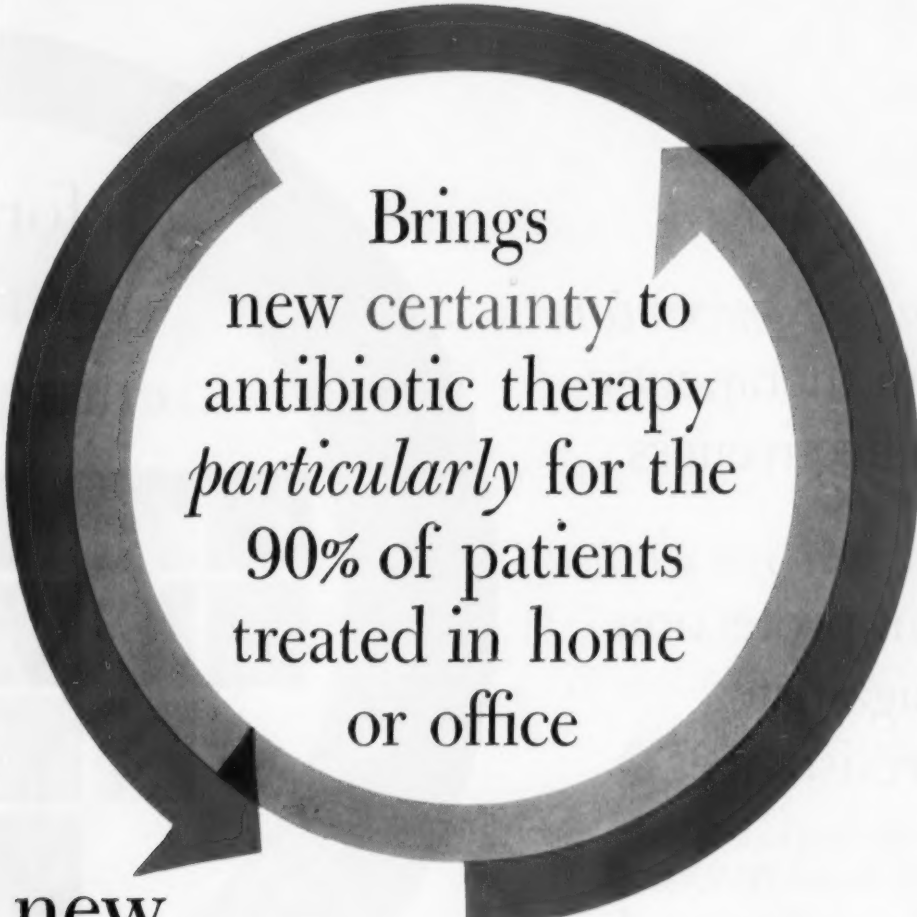
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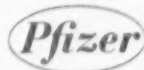
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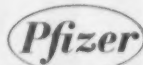
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Volume 1 • Number 11

November 1956

Oral Melanin Pigmentation In Intestinal Polyposis

Histopathologic Considerations

EDWARD V. ZEGARELLI, D.D.S., M.S., AUSTIN H. KUTSCHER, D.D.S.,
JOHN D. PIRO, D.D.S., and NORMAN KUPFERBERG, B.A.

IN 1949, Jeghers, McKusick, and Katz¹ again called attention to the diagnostic importance of an unusual familial disorder (previously described by and known as the syndrome of Peutz²) characterized by melanin spots of the lips and mouth and, to a lesser degree, of the skin, in association with polyposis of the intestine. Thereafter, numerous reports have established this syndrome as of considerable importance and not uncommon. The polyps, which are usually observed in the small intestine, may cause obstruction and intussusception or may undergo malignant degeneration.

With the exception of the material gathered together by Jeghers, McKusick, and Katz, these reports each have been concerned usually with only one or two cases. Jeghers, McKusick, and Katz described primarily the clinical and hereditary considerations in the absence of

From the Institute of Cancer Research, College of Physicians and Surgeons, Columbia University, New York City; the Division of Stomatology of the School of Dental and Oral Surgery of the Faculty of Medicine, Columbia University, New York City; and the Research Foundation of the State University of New York, College of Medicine at New York City, Brooklyn, N. Y.

This study was supported in part by grants-in-aid from Chas. Pfizer & Co., Brooklyn, N. Y., and A. H. Robins Co., Inc., Richmond, Va.

The authors express their deepest appreciation to the following investigators: Drs. M. L. Bradford, L. E. Danzig, J. T. Freeman, I. S. Ravdin, H. H. Wolff, H. Goldberg, M. R. Behrer, O. D. Fisher, A. I. Bortz, F. H. Bethell, R. Andrew, B. F. Perry, J. J. Zuska, C. R. Savage, N. C. Tanner, C. E. Moore, E. P. Vary, S. Sommers, H. Fangre, M. A. Troxell, F. Ronchese, and R. A. Weber. Without their most generous assistance this study would not have been possible.

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available pathologic material for many of their cases. A thorough review of the literature revealed that previously published material contained only fragmentary and uncorrelated information with regard to the histopathologic aspects of this syndrome. Therefore, we have made an attempt to gather together from the reporting investigators as much histopathologic material as was available, with the hope that intensive study of a larger body of material, all available for review at one time and by one group of investigators, might be rewarded by a more comprehensive understanding of this syndrome.

Accordingly, we entered into communication with the authors of each paper which had come to our attention, explaining our purposes and requesting their cooperation to the extent of providing us with any biopsy material still available. We thus came into possession of the biopsy material of 19 cases representing 15 reports. Five of the 45 reports dated back to the years between 1895 and 1925.

CLINICAL CONSIDERATIONS

A brief recapitulation of the facts surrounding this syndrome suggests a composite clinical picture of a relatively unusual familial disease in which, at an early age, melanin spots are found to be distributed peculiarly in and about the mouth. During the second and third decades pigmented spots may increase in number in the oral mucosa and skin, while intermittent abdominal pain, vomiting, melena, and anemia are seen in some individuals.

The polyps occur most frequently in the small intestine, although they may be widespread. Intestinal obstruction due to intussusception, initiated by polyps, frequently follows. Several patients have required multiple operations because of intussusception, and others have died as a result of intussusception. In nine patients⁴⁴ adenocarcinoma developed in one or more of the polyps. Malignant degeneration in this syndrome may, therefore, be a greater hazard than was suspected earlier.

This syndrome of pigmentation and polyps is thought to be familial and hereditary, following a simple Mendel-dominant inheritance, with both sexes equally affected. A strong tendency emerges, if a complete genealogic survey is made, for several cases of this syndrome to occur in the same family—some with the complete syndrome, some with pigmentation only.

The characteristic melanin spots may occur without demonstrable evidence of intestinal polyposis. Conversely, generalized or small-

Oral Melanin Spots in Intestinal Polyposis

TABLE 1. History and Data on 19 Patients with Oral Melanin Pigmentation and Associated Intestinal Polyposis

Case number	1 ^a	2 ^a	3 ^a	4 ^a	5 ^a	6 ^a	7 ^a	8 ^a	9 ^a	10 ^a	11 ^a	12 ^a	13 ^a	14 ^a	15 ^a	16 ^a	17 ^a	18 ^a	19 ^a
History																			
Family history	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.	Neg.
Duration (mo.)	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24	24
No. operations for intussusception	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Polyposis demonstrated at autopsy	Liv.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Severe periodic abdominal pain	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Vomiting or nausea	Occ.	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Bloody stools	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anorexia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Myalgia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Constipation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Anemia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sinusitis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lethargy	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Falor	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Diarrhea	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Weakness	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ulcer	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Abdominal enlargement	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nationality	Am.	Ital.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.	Am.
Sex	F	F	M	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F
Age	17	8	15	13	14	64	50	7	14	14	16	10	28	17	27	24	28	77	15
Polyp	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectosigmoid juncture	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nasal	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Cervical	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Adenocarcinoma	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Stomach	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Small intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Large intestine	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectum	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Rectosigmoid juncture	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

^a Described by Dr. S. Summers.

TABLE 2. Characteristics of the Pigmentation in 19 Patients with Oral Melanin Pigmentation and Associated Intestinal Polyps

Case number	1 ¹	2 ²	25 ³	4 ⁴	5 ⁵	6 ¹⁰	7 ¹²	8 ¹¹	9 ⁹	10 ¹²	11 ¹⁰	12 ¹⁰	13 ¹³	14 ¹⁰	15 ¹	16 ¹	17 ¹	18 ⁰	19 ³
Areas of pigmentation																			
Mouth (about)	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Palate, hard																			
Gingivae																			
Tongue																			
Oral mucosa (cheeks)																			
Alveolar ridges																			
Lips, mucosa	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Lips, outer	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Fingers	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Feet	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?	?
Toes																			
Cheek (skin)																			
Hands																			
Eyes																			
Forehead																			
Nose																			
Palm, heel, sternum, umbilicus																			
Neck						+													
Feet																			
Color of hair		D.B.	K.		B.	G.													
Color of iris	?	D.B.	L.		B.				B.	B.			+	+	D.B. D.L.	K. D.B. D.L.	D.B. D.L.		
Complexion			D.		D.	D.					D.								
Oral pigmentation (Color)																			
Brown						+				+									+
Blue																			
Black						+													
Slate blue																			
Gray																			
Are pigmentation first noted	?		C		M	54													
Are pigmentation first noted		+	M		?	28, 1A		Sm											
Family history pigmentation																			
Size (mm.), approx.										2-18	Sm	1-6							1-5

^a Reported by Dr. S. Sommers; not described.

D = Dark L = Blue G = Gray P

B = Brown K = Black F = Fair M

10

Oral Melanin Spots in Intestinal Polyposis

intestinal polyposis may have occurred without pigmentation, or its presence may have been overlooked for years.¹² The clinical importance of the oral and extraoral pigmentation lies primarily in its diagnostic value in suggesting the possibility of gastrointestinal polyp disease, especially in patients with periodic abdominal pain, unexplained anemia, and melena.

Since it was not the purpose of our work to further describe the clinical appearance or course of these lesions, our observations will be confined to histopathologic considerations.

The histories of all the patients whose biopsy specimens were studied in our laboratory have been summarized in Table 1 and the characteristics of pigmentation of these patients in Table 2. Bibliographic reference is made for further details of each case originally reported elsewhere.

HISTOPATHOLOGIC OBSERVATIONS

Polyps

Our investigation yielded the following pertinent histopathologic findings:*

Whether the polyps arose in stomach, small intestine, or colon, they presented an essentially similar appearance. They tended to form well-differentiated but irregular glandular structures producing moderate to abundant mucous secretion (Figs. 1 and 2). The epithelial cells usually showed good polarity and basement membranes were clearly seen. Occasionally, ulceration, hemorrhage, and nonspecific inflammation were manifest superficially. No pigment was present in any polyps, even those of the colon.

Where malignant change was present, the growths still showed a benign adenomatous pattern with carcinoma apparent only in the deeper portions of the mucosa or in penetrating glands. From this observation, in terms of the slides at our disposal, it may be possible to infer that, despite the variety and multiplicity of adenomatous polyp formation, malignant growth is likely to be well-differentiated, slow to invade, and apt to remain localized (Fig. 3). This assumption can only be verified by further extended study of such a group of patients over a long period of time.

* The sections were studied by Dr. Edith E. Sproul, Pathologist of the Francis Delafield Hospital, Columbia University, New York, N. Y.

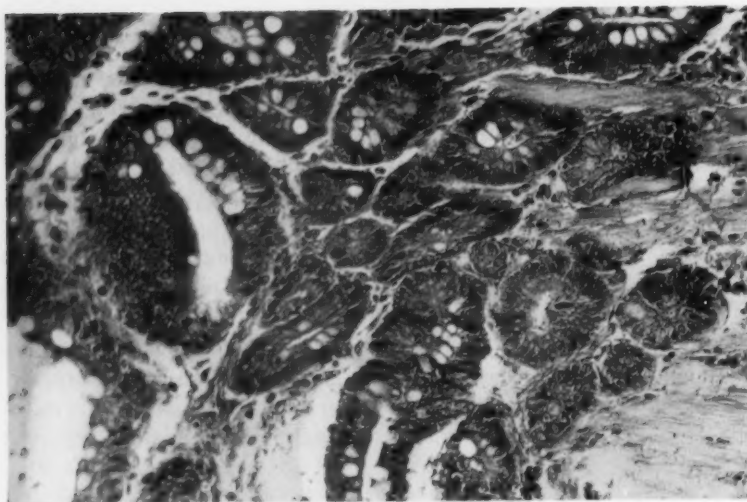


Fig. 1. Adenomatous polyp showing excessive mucous production in the glands.

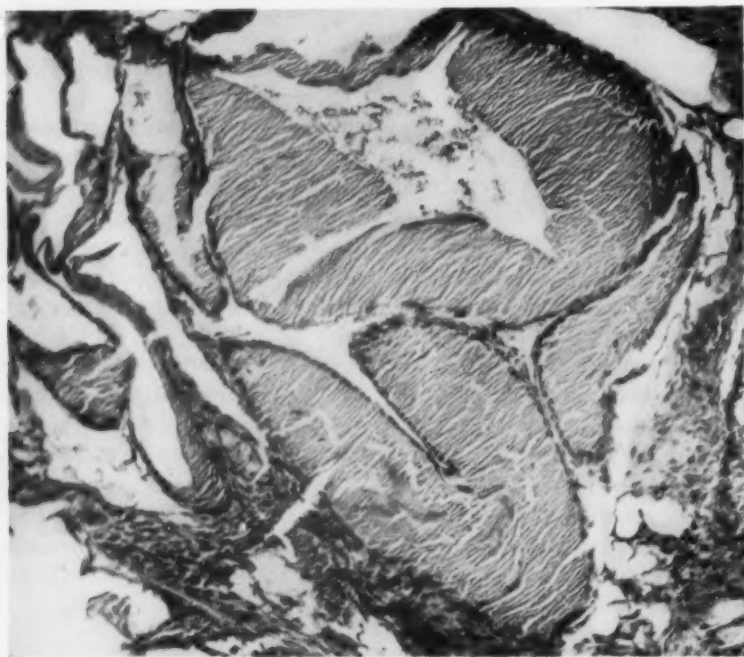


Fig. 2. Adenomatous polyp showing a moderate production of mucus.

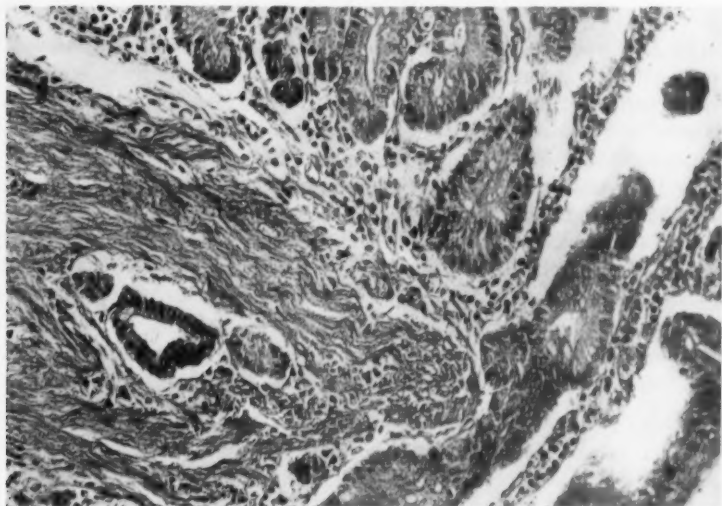


Fig. 3. Well-differentiated adenocarcinoma with glandular structures invading the depth of the muscle.

Pigmented Areas

With regard to the oral or circumoral pigmentation, biopsy specimens from three patients and a description of a fourth as it appears in the literature were the only ones available.

Biopsy specimens¹⁰ taken from three areas in one patient (in whom cervical and nasal but not gastrointestinal polyps have been demonstrated) revealed the following:

The pigmented skin from the side of the neck showed a thick layer of epidermis partly without rete pegs and with slight hyperkeratosis and edema. Perinuclear vacuolization of the basal and prickle cells was also seen. Along the basal layer there was a small amount of finely divided melanin, some of which appeared to be in the cells while other granules appeared to lie between them. An abundant amount of fairly coarse melanin was present in stellate chromatophores throughout the corium, but the distribution was patchy. The corium was further characterized by a loose infiltrate of lymphocytes and a few neutrophils, eosinophils, fibroblasts, and histiocytes. These cells mainly were near but not tightly clustered around the numerous small capillaries. The subcutaneous tissue was intact except for a few perivascular phagocytes.

A pigmented spot from the buccal mucosa revealed normal epithelium except for slight vacuolization of the basal and deep prickle cells. Scanty deposits of fine melanin granules were found between a few of the basal

cells. In the superficial stroma and within phagocytes were scattered small collections of melanin, and between these collections were several fairly dense infiltrations of lymphocytes and histiocytes. The stroma also appeared to be focally edematous, with an increase in the number of capillaries at one point. The deeper tissues were essentially normal.

A pigmented area on the gingiva showed the epithelium as normal in cellular pattern and depth and with considerable amounts of melanin in tiny granules along the basal layer. The supporting stroma contained large numbers of small blood vessels, about many of which were small infiltrations of plasma cells, lymphocytes, and histiocytes. Again, only small quantities of melanin were found in scattered foci in the stroma just beneath the epithelium.

Case 18

Troxell¹¹ biopsied a melanin spot occurring on the oral mucous membrane of the lower lip and described (with illustrations) the histopathology as follows:

The pigment seems largely restricted to a well demarcated portion of the basal layer. There is a marked variation in the degree of pigmentation within this portion. The dermal pigmentation largely underlies the epidermal pigmentation, which is largely confined to dendritic cells in the basal layer. . . . The "vertical band formation" reported as characteristic of the syndrome of Peutz has not been microscopically confirmed, and might well be identical with Becker's capping form or the columnar arrangement . . . observed in physiologic melanoplakia. . . . Jeghers' biopsy was of a palmar lesion, and palmar lesions are not an essential part of the syndrome. Even if they were, it cannot be assumed that oral and cutaneous lesions would show a comparable histopathologic picture.

Biopsy findings of a melanin patch on the gingivae were reported by Goldberg and Goldhaber³⁸ as follows:

On microscopic examination, the epithelium is of normal character except for one area of moderate acanthosis. There is pigmentation of a few cells of the basal cell layer, particularly at the tip of the "rete pegs." The subepidermal tissue shows some proliferation of connective tissue elements and areas of chronic inflammation. Several melanophores are present in the mid-corium.

The only other skin biopsy reported in the literature is that of a pigmented macule on the hypothenar portion of the right palm studied by Dr. Lloyd W. Ketron¹:

Although clinically the pigmentation seems to have a uniform and diffuse distribution, the sections reveal that the changes occur mainly in vertical bands. In these segments the following alterations are seen in the various layers: in the stratum corneum there are masses of melanin conforming

Oral Melanin Spots in Intestinal Polyposis

in size and shape with those of cells in most instances; in the basal layer there is an increased number of "clear cells" of Masson and perhaps also of the melanoblasts although none of the stains used demonstrate well the branching processes of these cells. Occasionally, one of the rete cells shows melanin granules, and a few cells in the granular layer have yellow-brown granules. In the cutis there are a moderate number of chromatophores and occasional extracellular accumulations of melanin. One gains the impression that there is slight proliferation of the fixed tissue cells around the superficial blood vessels, which also appear to be dilated. However, because of regional differences this cannot be said with absolute certainty. These changes are similar pathologically to those seen in lentigines. However, because of the age incidence and anatomic distribution, I should hesitate to place them in that group.

SUMMARY

Increasing attention has been devoted recently to the syndrome of oral melanosis with associated intestinal polyposis. An attempt was made to gather together biopsy specimens of polyps and pigmented lesions described in case reports of this syndrome in the hope that intensive study of a larger body of material might be rewarded by a more comprehensive understanding of this syndrome.

The limited histopathologic findings concerning pigmented skin and oral mucous-membrane areas have been reviewed. There is a paucity of biopsy material obtainable from such areas which are pathognomonic but free of disturbing symptoms.

Our observations on the intestinal polyps suggest that whether they arose in stomach, small intestine, or colon, they presented an essentially similar appearance—well-differentiated but irregular glandular structures producing moderate to abundant mucous secretion. Occasionally ulceration, hemorrhage, and nonspecific inflammation were manifest superficially. No pigment was present in any polyps, even those of the colon.

Where malignant change was present, the growths still showed a benign adenomatous pattern, with carcinoma apparent only in deeper portions of the mucosa or in penetrating glands. It may be possible to infer that malignant growth is likely to be well differentiated, slow to invade, and apt to remain localized. This assumption can only be verified by further careful study of a group of patients over a long period of time.

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Cholografin Methylglucamine

New Contrast Medium for Intravenous Cholangiography and Cholecystography

WILLIAM H. SHEHADI, M.D., and ISSA SABBAG, M.D.

CHOLOGRAFIN methylglucamine* (methylglucamine iodipamide) is a new, improved, contrast medium for rapid visualization of the biliary tract following intravenous injection. Superseding Cholografin (sodium iodipamide), it is similar to it in structure, with the methylglucamine radical replacing the sodium. The methylglucamine salt of iodipamide is far more soluble than either the sodium salt (Chlorografin) or the lithium salt.† The latter, which was investigated in this department some time ago, has been withdrawn by the manufacturer because of its high toxicity.

Cholografin methylglucamine has the same indications and contraindications as does Cholografin.^{1-10, 12} It is, however, a superior contrast medium for rapid visualization of the biliary tract because of the following:^{9, 11, 12} (1) a markedly lower incidence of side reactions; (2) a greater ease of administration through smaller total volume of the required dose; and (3) at times, improved visualization of the biliary tract. It may be wise, however, to delay full evaluation of the latter observation until we gain a fuller understanding of the mechanisms of liver function and its relation to the excretion of Cholografin and Cholografin methylglucamine. At any rate, under identical conditions the biliary tract is visualized at least as well with Cholografin methylglucamine as it is with Cholografin, if not better.

CHEMICAL PROPERTIES

Cholografin methylglucamine is the methylglucamine salt of N,N'-adipyl-bis(3-amino-2,4,6-triiodobenzoic acid).

From the Department of Radiology, The New York Polyclinic Medical School and Hospital, New York, N. Y.

* Cholografin methylglucamine was supplied by the Department of Medical Research, E. R. Squibb & Sons, New York, N. Y.

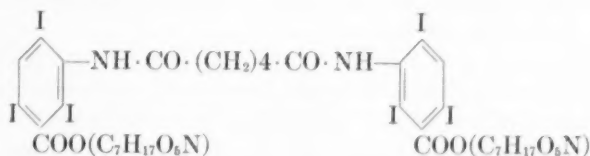
† Supplies of this contrast medium were provided by Schering, A. G., West Berlin.

Cholografin Methylglucamine

TABLE 1. Side Reactions Observed in 100 Patients after Injection of 20 cc. Cholografin Methylglucamine and 100 Patients after Injection of 40 cc. Cholografin

		Nau- sea	Vom- iting	Sen- sation of heat and flush- ing	Faint- ness	Head- ache	Itch- ing	Chills	Fever	Pain in arm dur- ing injec- tion	Total side reac- tions
Cholografin methyl- glucamine (52%)	4	1	3	2	0	0	0	0	0	0	10
Cholografin (20%)	6	2	6	0	1	1	2	1	3	22	

The empirical formula is $C_{20}H_{14}O_6N_2I_6 \cdot (C_7H_{17}O_5N)2 \cdot 3H_2O$ and the structural formula is



The molecular weight of this compound is 1584, the iodine content is approximately 48 per cent. The iodine element is firmly bound in the molecule.

Cholografin methylglucamine is several times more soluble than the sodium salt and approximately twice as soluble as the lithium salt.^{13, 14} It presents a clear colorless solution, and is supplied in 20 cc. ampules of 52 per cent, which is the optimal dose, together with a companion 1 cc. test ampule. The pH is 6.0-6.5. We have investigated a solution with a pH of 7.0-7.5 and have found it equally satisfactory.

PREPARATION OF THE PATIENT

The patient is prepared as previously recommended when Cholografin is to be used—by dehydration by withholding fluids for at least 12 hours prior to the examination and the administration of a dose of castor oil at bedtime, the night before. Strict adherence to these recommendations greatly improves the results of the examination.

TECHNIC OF ADMINISTRATION and SIDE REACTIONS

Here, again, the technic of administration is essentially the same as that used for Cholografin. While the toxicity and incidence of side

reactions are almost negligible as compared with the sodium (Table 1) and lithium salts^{9, 12, 14} under no circumstances should caution in the administration of this contrast medium be relinquished. As in the case of intravenous urography, preliminary testing is of little or no value and is unreliable in predicting the occurrence of side reactions.^{8, 9, 16} A negative test should not lull us into a false sense of security.

Among the chief contraindications are obstructive jaundice and severe liver and kidney disease. A history of an unfavorable reaction to prior intravenous urography or cholangiography calls for increased caution. A history of allergy as such is not necessarily a contraindication. In these cases, premedication with antihistaminics often proves adequate. Nevertheless, at all times an emergency set should be constantly available in the radiographic room at the time of injection, and should consist of at least the following: a number of sterile syringes and needles, Chlor-trimeton or Benadryl, ephedrine, 5% sterile glucose solution, and an oxygen tank.

Several patients who experienced side reactions of varying intensity following the injection of Cholografin experienced no definite side reactions upon repetition of the examination using Cholografin methylglucamine. Slow administration reduces the incidence as well as the intensity of side reactions. The total dose should be injected in from 8 to 10 minutes.

There is no local reaction when accidentally injected into the soft tissues outside a vein. Likewise, there is no venospasm and no pain along the arm during the injection. There was no significant change in the blood pressure as determined before, during, and after the injection.

MATERIAL STUDIED

This report is based on the examination of 100 nonselected patients referred to our Department of Radiology for routine examination of the biliary tract. Fifty patients were known to have no previous surgical operations on the biliary tract, and the other fifty patients had undergone cholecystectomy 10 days to 22 years prior. There were 63 female and 37 male patients. The youngest, a female, was 26 years old, and the oldest, a male, was 83 years old.

OBSERVATIONS

The findings, summarized in Tables 2 and 3, may be considered not unlike those in any cross-section of patients in a comparable series.

Cholografin Methylglucamine

TABLE 2. Summary of Findings in 50 Noncholecystectomized Patients Examined with Cholografin Methylglucamine

Examination		Operative findings
Telepaque and Cholografin methylglucamine	36	
Visualized with Telepaque and Cholografin methylglucamine	10	
Normal		6 Not operated on
Abnormal (poor visualization with multiple calculi)		4 Chronic cholecystitis with calculi
Visualized with Cholografin methylglucamine and not with Telepaque	11	
Normal		7 Not operated on
Abnormal		4 Chronic cholecystitis with calculi
Poor visualization with multiple calculi	2	
Calculus in infundibulum	1	
Calculus in infundibulum and calculus impacted in dilated cystic duct	1	
Cholografin methylglucamine only	15	
Gallbladder visualized	7	Not operated on
Normal	5	
Abnormal	2	
Poor visualization with calculi in gallbladder and common duct	1	
Good visualization, Phrygian cap deformity, multiple calculi	1	
Gallbladder not visualized	8	Chronic cholecystitis with calculi

TABLE 3. Summary of Observations on the Ducts in 100 Patients Examined with Cholografin Methylglucamine

	Visual- ized	Normal	Dilated	Not visual- ized	Patients with jaundice
A. Duct Visualization					
Noncholecystectomized					
50 patients	36	33	3	14	11
Cholecystectomized					
50 patients	35	13	22	15	12
B. Pathological conditions noted in cholecystectomized patients					
"Reformed" gallbladder					2
Residual cystic duct					2
Transitory spasm of sphincter of Oddi evidenced by changing caliber of ducts					2
Stricture of sphincter of Oddi					4
Penetrating duodenal ulcer with accompanying dilatation of duct					1
Calculi in the common bile duct					4
Dilatation without demonstrable cause					10

The excretion pattern is practically identical with that of Cholografin. Not less than 90 per cent is excreted by the liver and, in the absence of impaired liver function, a maximum of 10 per cent is excreted by the kidneys. Simultaneous hepatic and renal excretion (Fig. 1) occurs in 50 per cent of the cases examined with no disturbance of biliary-tract visualization and without decrease in the intensity of the shadow of the bile ducts, or of the gallbladder when present. Excretion is almost entirely renal in cases of marked liver disease.



Fig. 1. Forty minutes after injection of 20 cc. Cholografin methylglucamine (52%). Simultaneous hepatic and renal excretion. Note renal pelvis (arrow 1) and normal bile duct (arrow 2). Early gallbladder filling. Slow diffusion of Cholografin methylglucamine in gallbladder. Note increased concentration along wall and upper portion of gallbladder (arrows).

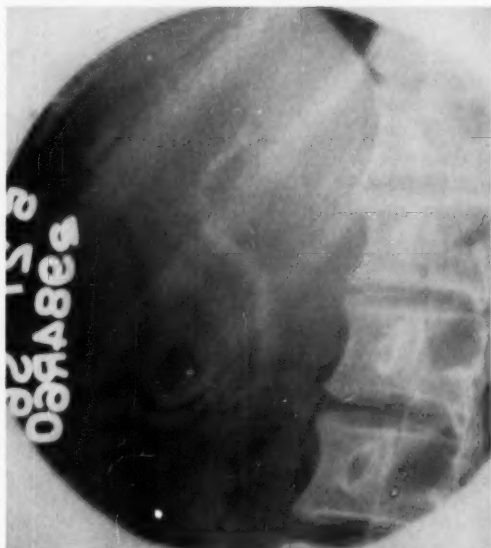


Fig. 2. Sixty minutes after injection of 20 cc. of Cholografin methylglucamine (52%). Normal bile ducts: normal gallbladder, rather early filling. Note free flow of the contrast medium into the duodenum. **Fig. 3.** Sixty minutes after injection of 20 cc. of Cholografin methylglucamine (52%). Hepatic and common bile ducts well visualized, caliber within the limits of normal. Cholecystectomy 17 years prior.

There has been no demonstrable hepatic excretion in cases of obstructive jaundice. However, in the two cases of severe hepatitis initial absence of hepatic excretion, with no biliary-tract visualization during the height of jaundice, became normal when jaundice subsided. Once excreted by the liver Cholografin methylglucamine travels rapidly through the small intestines and reaches the ascending colon in a maximum of three hours. There is no absorption from the intestines.

In the normal subject, hepatic excretion is prompt and bile-duct visualization occurs in less than 10 minutes. Films should be made at 10-minute intervals up to 60 minutes. The bile ducts are best visualized at about 30-60 minutes after injection (Figs. 2 to 5). Each film should be carefully inspected before the next one is made. The position of the patient and technic should be modified or corrected, when necessary, until excellent visualization of the ducts is obtained. Optimal gall-bladder visualization occurs at 2-2½ hours. Frequently this occurs



Fig. 4. Thirty minutes after injection of 20 cc. Cholografin methylglucamine. Cholecystectomy 3 years prior. Dilated common and hepatic bile ducts. Residual cystic duct (arrow 2). Note contrast medium in descending duodenum, with reflux into the duodenal bulb (arrow 1), simulating a small gallbladder. This is easily ruled out because of its absence in other films (not shown here) and because of the location of the residual cystic duct (arrow 2).

Cholografin Methylglucamine

within the first hour (see Figs. 1 and 2). The subsequent examination of the gallbladder should be completed in the usual manner.

Recently we have noted a steady rise in the incidence of early gallbladder visualization which is attributed to the routine administration of a meal containing simple fats on the evening preceding the examination. This simple method of preliminary biliary drainage, used routinely in this department with both the oral and intravenous methods has

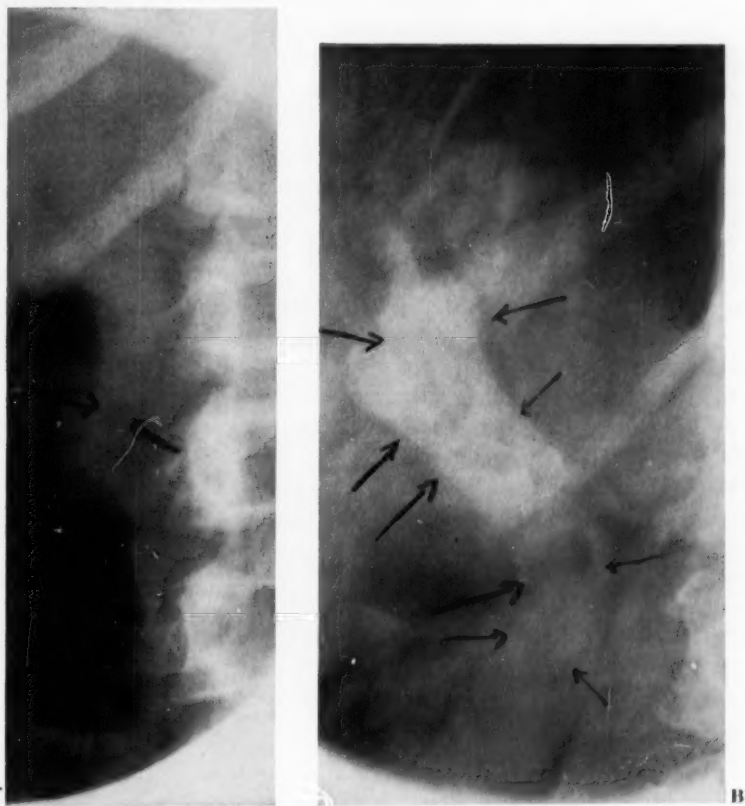


Fig. 5. A, Cholecystectomy 10 years prior. Recurrent jaundice. Forty minutes after injection of 20 cc. Cholografin methylglucamine (52%). Note 0.5 X 1.0 cm. filling defect at distal end of dilated common bile duct representing a cholesterol calculus; proved at operation. B, Cholecystectomy 12 years prior. Two hours after injection. Slow visualization of markedly dilated hepatic and common bile ducts. Multiple filling defects representing cholesterol calculi; proved at operation.

brought about an increase in the incidence of gallbladder visualization, especially when the gallbladder had failed to visualize on previous examinations.

Slow and irregular diffusion of Cholografin methylglucamine into the gallbladder will result in unequal admixture with the bile (See Fig. 1), producing a variety of irregular and unusual patterns. Serial films will show a gradual disappearance of these shadows, a more uniform filling of the gallbladder with the contrast medium, proving the absence of a constant defect and ruling out the presence of a calculus.

SUMMARY and CONCLUSIONS

Cholografin methylglucamine, a recently introduced contrast medium for rapid intravenous cholangiography and cholecystography, is a definite improvement over Cholografin.

Its chief advantages are a low incidence of side reactions, greater ease of administration through smaller total volume of the required dose, and, at times, improved visualization of the biliary tract.

The use of Cholografin methylglucamine, replacing Cholografin, is indicated:

- In patients who have had prior cholecystectomy.
- When the gallbladder fails to visualize following oral administration of an opacifying medium.
- When due to disturbed function or disease of the gastrointestinal tract, the patients are unable to retain or absorb orally administered medication.
- For prompt evaluation of the biliary tract in the differential diagnosis of acute abdominal conditions.

The contraindications, the same as for Cholografin, are obstructive jaundice and severe liver and kidney disease.

The introduction of Cholografin methylglucamine represents definite progress in the roentgen visualization of the biliary tract.

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Correction

In the article "Esophageal Varices Caused by Metastasis of Carcinoma to the Liver," page 145 of the April, 1956, issue (Vol. 1., No. 4), two illustrations have been described incorrectly. Figure 1 depicts the esophagus from Case 2, Fig. 3 that of Case 1.

Annular Pancreas

Roentgen Manifestations

MAXWELL H. POPPEL, M.D., and SAMUEL L. BERANBAUM, M.D.

IT IS THE PURPOSE of this paper to describe and illustrate the roentgen manifestations of 16 surgically verified cases of annular pancreas.

Annular pancreas was first described by Ecker in 1862. To date, 94 cases have been reported, most in the last two decades. Although a rare congenital anomaly, it is not quite as infrequent as previously considered. Improved roentgen diagnostic accuracy will undoubtedly increase the incidence.

EMBRYOLOGY

Annular pancreas is a congenital anomaly of indefinite origin. The most likely explanations are:

It results from the persistence of the left half of the ventral anlage of the pancreas which ordinarily atrophies.

The left lobe of the ventral pancreas grows around the duodenum to join the dorsal pancreas, so that the duodenum is encircled by pancreatic tissue.

The uncinate process or other portion of the head of the pancreas partially or completely encircles a portion of the duodenum.

PATHOLOGY

In one type of annular pancreas there are two arms (anterior and posterior) of pancreatic tissue found around the descending duodenum. In some there is a gap which is more apt to appear anteriorly. In others there is an encircling ring of pancreatic tissue. The encircling pancreas often is normal pancreatic tissue. Pancreatitis may be present and may be the cause of death. In one case carcinoma of the head of the pancreas was also present (Fig. 1A). In another case carcinoma actually developed in the annular pancreas (Fig. 1B).

Secondary dilatation of the stomach and duodenum are the result of obstruction.

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Annular Pancreas

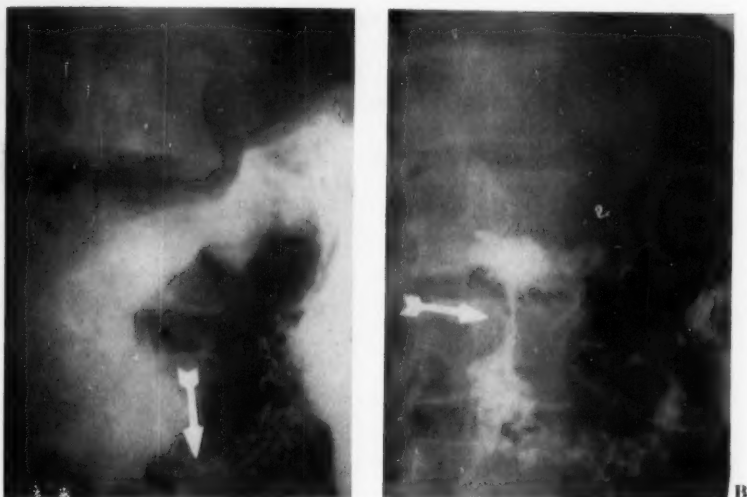


Fig. 1. *A*, arrow points to an annular pancreas. In addition, a carcinoma of the head of the pancreas produced a definite narrowing of the duodenum. *B*, marked narrowing which resulted from a carcinoma in an annular pancreas.

The duct draining the encircling pancreatic tissue usually opens independently into the duodenum. Derangement of the lower biliary tract is sometimes found. Biliary obstruction generally does not appear. If present, it is apt to manifest itself in infancy. As with other congenital anomalies, associated anomalies may be present in other parts of the body.

Although annular pancreas is a congenital anomaly, the majority of the reported cases are in adults. Kantor's dictum is worth repeating:

Anomalies may cause symptoms in some of their bearers all the time, in some of their bearers some of the time, but are under no obligation to cause symptoms in all of their bearers all the time.

There are three clinical types: (1) those producing duodenal obstruction so complete that surgery is essential a few days after birth; (2) those in whom duodenal obstruction does not occur till late in life; (3) those in whom duodenal obstruction is minimal or nonexistent, and the annular pancreas is an incidental finding at autopsy.

RADIOLOGIC FEATURES

Preoperative diagnosis depends on a high incidence of suspicion of the clinical symptoms. But most important is an appreciation of the

Poppel & Beranbaum

roentgenologic diagnostic criteria. The composite radiologic features of 16 surgically verified cases are presented (Figs. 2-5). Two illustrative case histories are included.

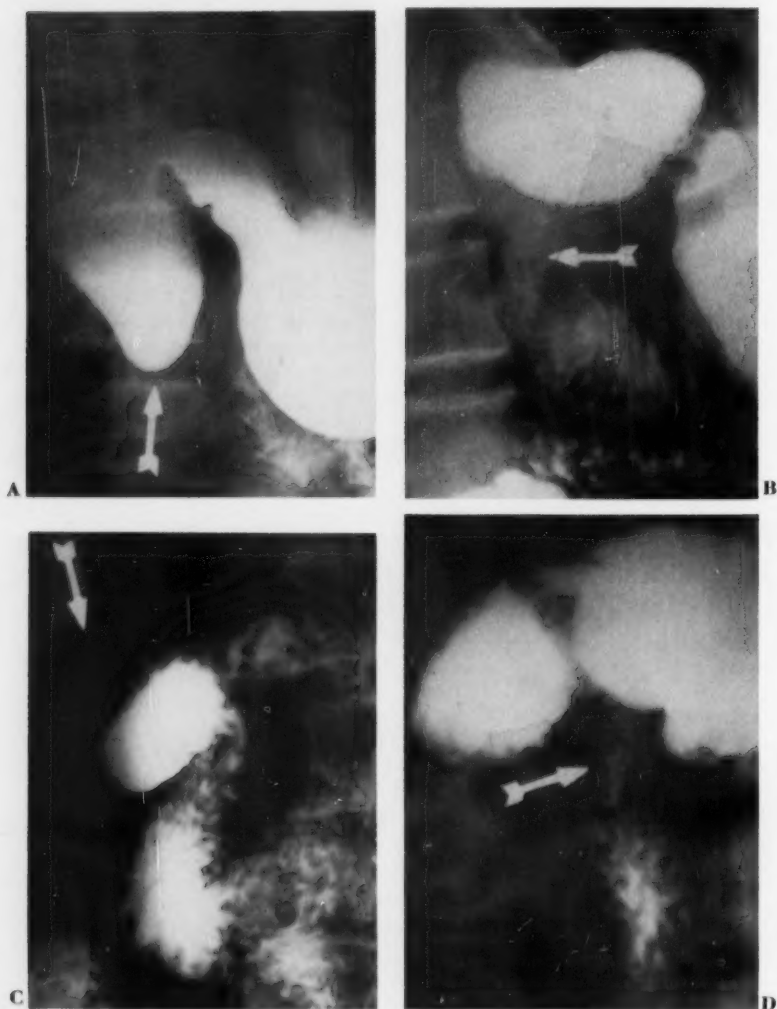


Fig. 2. *A*, arrow points to obstructive segment produced by annular pancreas. *B, C, D*, three cases of annular pancreas (arrow).

Annular Pancreas

Case 1

L. W., a 57-year-old white male, was admitted with postprandial nausea, which was especially severe after a heavy meal. Vomiting occurred about twice a week. The vomiting occurred in the evening, between 9:00 P.M.

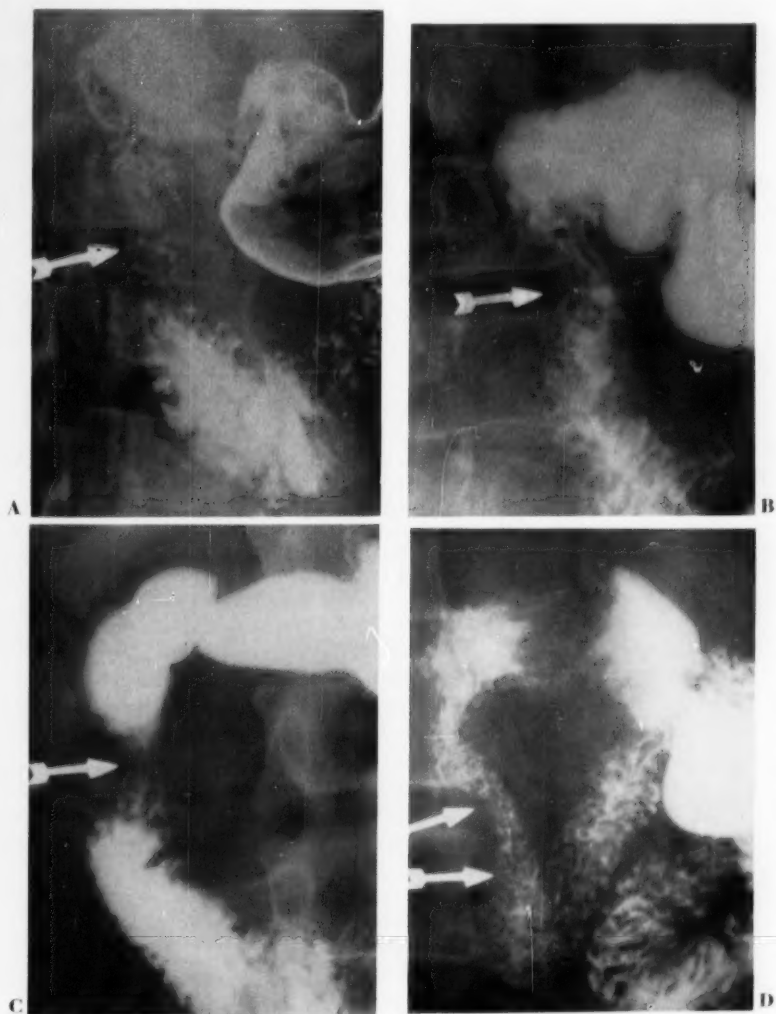


Fig. 3. A, B, C, D, four cases of annular pancreas (arrow).

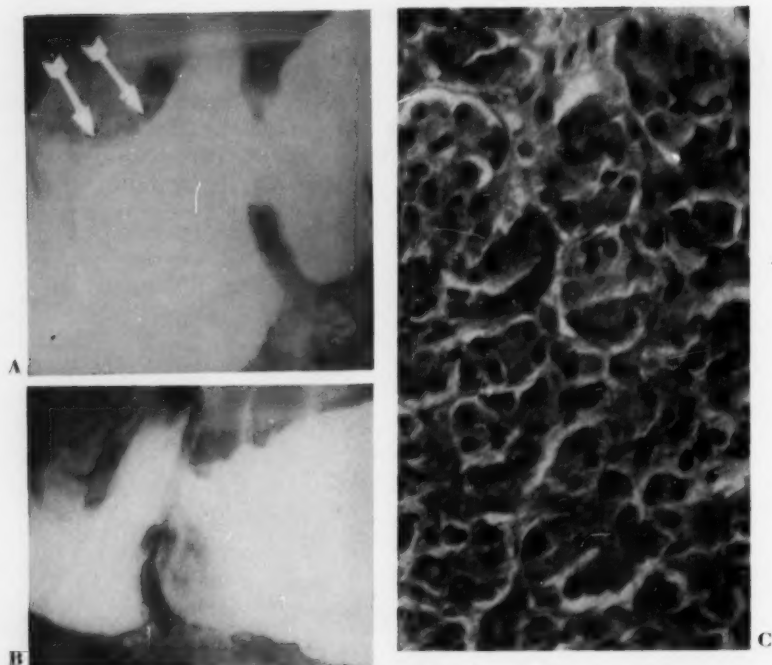


Fig. 4. A, arrows point to annular pancreas just beyond the bulb. This is a pre-operative film (courtesy of Dr. Samuel Glasser, Oklahoma City). B, appearance 10 months after operation. The lumen is practically normal. There is no obstruction. C, microscopic appearance of annular pancreas.

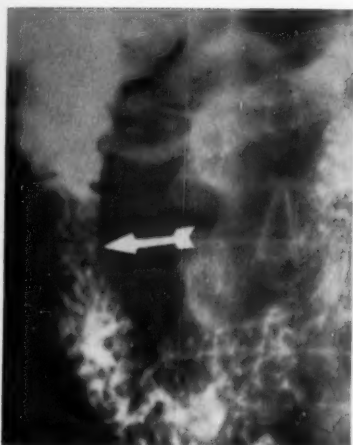
and midnight. There was no pain, no change in bowel habits, nor any rectal bleeding. He was in good health and had recently gained five pounds.

Physical examination was negative. Laboratory work-up was negative. A gallbladder series was normal. The gastrointestinal series showed moderate extrinsic pressure on the descending duodenum which was constant in all positions. The narrowed segment was smooth in outline, but the mucosal folds seemed smaller than normal (Fig. 6A).

At operation an annular pancreas was found. After mobilization of the duodenum a duodenojejunostomy was performed.

Case 2

C. M., a 68-year-old white female, complained of right upper-quadrant pain intermittently for 3 to 4 months. Infrequent similar pain had been noted for 6 to 8 years, occurring about one hour after meals. Physical examination was negative. Laboratory studies were noncontributory. Oral cholecystography was negative.



A



B

↑ Fig. 5. *A, B, C*, three cases of annular pancreas (arrow)



C

↓ Fig. 6. *A* (Case 1), arrow points to annular of the pancreas. Note under-developed mucosal folds. *B* (Case 2), arrow points to markedly narrowed segment produced by encircling pancreas (courtesy of Dr. John F. Roach).



A



B

Poppel & Beranbaum

The gastrointestinal series initially failed to visualize the complete duodenum in spite of all maneuvers. The bulb was only partially filled. At 6 hours there was considerable gastric retention. At this time there was seen a large, smooth, concentric, postbulbar narrowing, with obstruction and smallness of the distal portion of the duodenum (Fig. 6B). At operation an annular pancreas was found.

DISCUSSION

The common roentgen denominator in all 16 cases is duodenal obstruction. This is due to a narrowed segment which is seen in every film and on fluoroscopy. The caliber of the reduced lumen is unaltered by any posture, respiratory phase, pressure, straining, coughing, or stage of digestion. There is no tenderness, no irritability, and no intolerance to the barium. No destruction of the mucosa is present. There is no change on repeat studies. The mucosal folds at the narrowed segment are smaller because they never grew to adult size, and when the encircling tissue is released at surgery there is no immediate change in caliber of the duodenal segment. It takes several weeks for this area to dilate up to normal.

The significant features are the large, smooth, dilated bulb and the dilated duodenum proximal to the annulation, as well as the uniform, constant, concentric, smooth constriction.

Differential Features

In postbulbar duodenal ulcer, irregularity, irritability, eccentricity, and lack of smooth uniformity are the outstanding differential features. Similarly, duodenal neoplasm reveals an eccentric space-occupying filling defect. Pancreatic neoplasm also shows eccentricity, external-pressure defect, and an increase in the retrogastric space as visualized in lateral films.

In addition, the large size of the duodenal bulb in annular pancreas indicates benign obstruction, permitting the dilatation to occur over a long period of time. In the other conditions megabulbus is not a feature. Congenital megabulbus without obstruction offers no diagnostic difficulty.

The clinical aspect of the case may at times aid in the diagnosis; for example, absence of occult blood in the stool and absence of stigmata of carcinoma (anemia, cachexia, etc.).

In infants the diagnosis offers less difficulty, purely because the possibility of a congenital lesion such as annular pancreas is more

Annular Pancreas

often considered in the differential diagnosis. Simple films of the abdomen in the horizontal and upright postures are sufficient to make the diagnosis. Indeed, barium studies are contraindicated. A helpful roentgenologic sign is the "double bubble sign," one bubble being the stomach, and the other the dilated proximal duodenum. If duodenal obstruction is established, it may be helpful to aspirate the gastric contents and inject 30 cc. of air before filming.

Duodenal atresia is the most important differential diagnosis to be considered. In atresia obstruction is complete. In annular pancreas it is conceivable that a small streak of gas may be seen distal to the point of obstruction, and therefore aid in the correct diagnosis.

CONCLUSIONS

The roentgenologic features of annular pancreas have been emphasized and illustrated.

A greater awareness of these features will result in a greater number of accurate preoperative diagnoses.

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CASE REPORT

Pseudomembranous Enterocolitis Due to Staphylococcal Infection and Intestinal Obstruction

VICTOR W. GROISSER, M.D.

THE PRESENT REPORT concerns the occurrence of acute pseudomembranous enterocolitis in a patient in whom intestinal obstruction and *Staphylococcus aureus* infection of the bowel were prominent etiologic features. Whereas the role of the latter has become well known in this disorder, the importance of intestinal obstruction in a small but noteworthy number of cases, with or without staphylococcal infection, is not widely appreciated. Since acute pseudomembranous enterocolitis occurs most frequently as a postoperative complication, it is of further interest that this patient had no recent surgery.

A 70-year-old white female first entered Mount Sinai Hospital with a chief complaint of fever of 1 day's duration. Five years prior to admission the patient began to note an increased susceptibility to upper respiratory infections. At this time she was completely investigated by her physician, who found her to have an hypoplastic bone marrow on sternal aspiration, associated with an anemia, leukopenia, and a variable thrombocytopenia in the peripheral blood. The previous medical history was negative and no obvious cause for the bone-marrow involvement could be discerned. Initially, occasional transfusions were required to maintain the hemoglobin in a range of 6 to 9 Gm./100 cc., but in the year prior to admission the patient required two units of packed cells approximately every three weeks, totaling 240 transfusions in five years. Cortisone and vitamin B₁₂ had no effect upon her hematologic picture. Three years prior to admission, the patient's skin became gradually darker in color and she developed mild diabetes mellitus, controlled by diet. One and a half years prior to admission she developed homologous serum jaundice secondary to one of her transfusions, and was treated successfully over a three-week period.

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Pseudomembranous Enterocolitis

The immediate cause for hospitalization was the sudden development on the day prior to admission of a pleuritic left chest pain associated with cough and a temperature elevation to 100°F.

PHYSICAL EXAMINATION

Significant physical examination on admission revealed a temperature of 101°F.; blood pressure 110/60 mm. Hg; pulse rate 96; and respiratory rate 28. The patient was a well-developed white female appearing acutely ill. She was somewhat disoriented, but responsive to commands. Her skin was an ashen, gray-blue color. There was moderate pallor but no purpura. The oropharynx was slightly injected. No significant adenopathy was felt. There were fine inspiratory rales at both lung bases and bronchial breath sounds at the left base. The heart was slightly enlarged to percussion and a Grade I systolic blowing murmur was heard diffusely over the precordium. The liver was enlarged and tender and extended down five fingers below the right costal margin. The spleen was not palpable. The remainder of the physical examination was normal.

LABORATORY STUDIES

Urinalysis showed a persistent trace albuminuria. The initial hemoglobin was 7 Gm./100 cc., but rose to 10 Gm./100 cc. after several transfusions. The total white count on admission was 1100 per cu. mm. with a differential count consisting of 20 per cent segmented neutrophils, 38 per cent bands, and 42 per cent lymphocytes. No immature cells were seen. The white count taken on the day of the patient's death was 4450 per cu. mm. with several myelocytes and metamyelocytes present. The platelets numbered 70,000 per cu. mm.; reticulocytes 2 per cent; erythrocyte sedimentation rate 100 mm. in 1 hour. The blood chemical determinations were as follows: blood urea nitrogen 26 mg./100 cc.; fasting blood sugar 121 mg./100 cc.; albumin 2.7 Gm./100 cc.; globulin 3.5 Gm./100 cc.; total bilirubin 1.5 mg./100 cc.; total cholesterol 225 mg./100 cc.; cholesterol esters 155 mg./100 cc.; alkaline phosphatase 3.5 King-Armstrong units; cephalin flocculation 4 plus. A blood culture revealed no growth. *Bacillus subtilis* and *Staphylococcus albus* B were found on culture of the nasal secretions. A throat culture grew *Streptococcus viridans*, *Staphylococcus albus* B and *Bacillus subtilis*. Urine culture, febrile agglutinins, heterophile antibody, and a Coombs test were all negative. Serum iron and total iron-binding capacity of the serum were both 160 µg./100 cc. Chest x-ray revealed a left paracardiac pulmonary infiltration and a slight enlargement of the transverse diameter of the heart. A left ventricular strain pattern was seen on electrocardiogram.

HOSPITAL COURSE

On admission, the patient was considered to have an acute bronchopneumonia superimposed on an aplastic anemia of undetermined etiology. She was treated with parenteral fluids and antibiotics. The latter consisted of streptomycin 1 Gm. a day for 6 days and tetracycline 0.5 Gm. administered in the intravenous fluid for the first 4 days and 1 Gm. in divided doses orally on the fifth and sixth hospital days. On this regimen the temperature fell from levels of 102° F to 99° F. The patient appeared symptomatically improved. She was better oriented, less dyspneic, and the lung findings were minimal. On the seventh hospital day she suddenly complained of epigastric pain and vomited twice. She then developed a marked watery diarrhea. It was felt that the antibiotics might in some way be related to these symptoms, and both the tetracycline and streptomycin were immediately discontinued. A stool specimen was sent for culture and sensitivity studies. Gram stain on the stool smear revealed gram-positive cocci. A presumptive diagnosis of a staphylococcal enteritis was made and the patient was immediately started on intravenous erythromycin. One day after the onset of the massive diarrhea the patient developed circulatory collapse, with a blood pressure of 60/0 mm. Hg and a pulse rate of 120 per minute. Her temperature rose to 104° F. Despite aggressive fluid and electrolyte replacement, the use of blood transfusions, and the administration of Levophed, the patient remained in shock and was pronounced dead on the ninth hospital day, 48 hours after the onset of the gastrointestinal disturbance. Subsequently, the stool culture was reported as being positive for *Staphylococcus aureus* and *Streptococcus fecalis*.

AUTOPSY FINDINGS

At autopsy there was a severe peptic esophagitis. The mucosa of the esophagus was dark grayish-violet in color and many superficial mucosal erosions were present, particularly near the esophagogastric junction. There were 500 cc. of fluid in the peritoneal cavity. All loops of small bowel were markedly distended, showing a mottled violaceous color on the serosal surface. The stomach and duodenum were normal. The small intestine from the ligament of Treitz to 12 cm. from the ileocecal valve was markedly dilated. At the latter location, there were fibrous adhesions extending to the old lower midline abdominal hysterectomy scar, producing a constriction of the ileum (Fig. 1). The wall of the jejunum and ileum down to this level was markedly thickened and the mucosa was covered by a grayish-yellow pseudomembrane (Fig. 2) which could be easily stripped off, leaving a red, granular surface. There were several small scattered patches of a similar membranous exudate 1-2 cm. distal to the obstruction. The terminal few centimeters of ileum, ileocecal valve, and the colon appeared grossly normal, without evidence of any membrane formation. The appendix, ovaries, fallopian tubes, and uterus were surgically absent.

Pseudomembranous Enterocolitis



Fig. 1. Cecum and terminal ileum at necropsy. The point of partial obstruction of the ileum due to a fibrous band is indicated by the arrow. Most of the pseudomembrane immediately proximal to this point has been stripped away.

Microscopic examination revealed desquamation of most of the mucosa of the esophagus, with massive infiltration of the submucosa by neutrophils, plasma cells, and lymphocytes. The submucosa of the jejunum and ileum up to the area of narrowing was markedly thickened, edematous, and massively infiltrated by neutrophils and some plasma cells and lymphocytes. Overlying this was a thick membrane comprised of fibrin, neutrophils,

necrotic mucosa, bacteria and bacterial colonies, and debris (Fig. 3). In several areas the mucosa was only partially necrotic. The necrosis and inflammation was most severe in the jejunum and lessened somewhat as one progressed distally into the ileum. Gram stain revealed the bacteria to be gram-positive cocci resembling staphylococci. The colon was normal microscopically except for an acute nonmembranous proctitis without necrosis.

The heart, lungs, liver, spleen, adrenals, kidneys, thyroid, pancreas, and lymph nodes revealed severe hemosiderosis. There was marked periportal fibrosis of the liver and fibrosis of the pancreas. Hemosiderin was found in the Kupffer cells, liver cells, and epithelial cells of the bile ducts.

The bone marrow was full. There was a marked diminution in the erythroid elements but an increase of the myeloid series. There was a maturation arrest of the white blood cells, with many promyelocytes and myeloblasts and few mature neutrophils. There was a marked increase of megakaryoblasts and megakaryocytes.

DISCUSSION

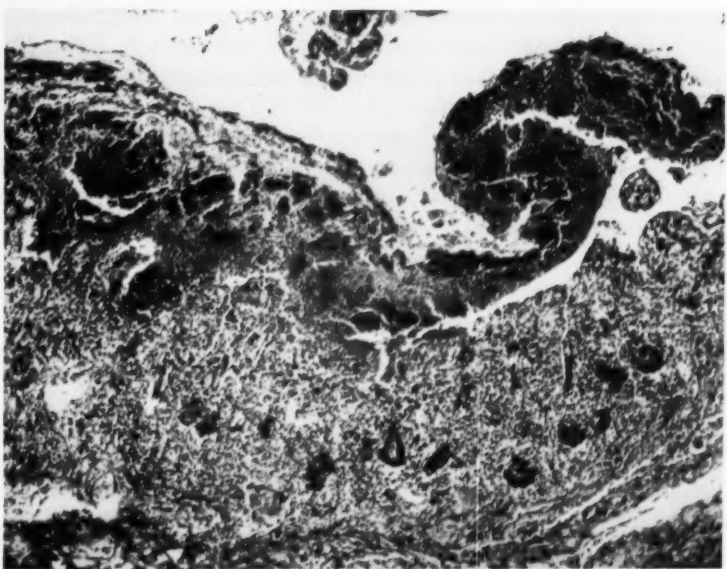
During the past five years the most uniform finding in cases of pseudomembranous enterocolitis has been the overgrowth of *Staphylococcus aureus* in association with the absence or marked suppression of the normal intestinal bacterial population.¹⁻⁵ This has been considered a consequence of extensive antibiotic therapy. The pathologic effects of the staphylococci are believed to be the result of enterotoxin formation. Just as in the era before antibiotics and chemotherapeutics, the lesions have developed primarily in the postoperative patient, particularly following abdominal surgery.

In the case herein described the almost abrupt termination of the mucosal necrosis at the point of constriction of the ileum suggests that obstruction as well as staphylococcal infection contributed significantly to the intestinal changes. In necropsy records of 14 nonsurgical and 94 postoperative patients with pseudomembranous enterocolitis reviewed at the Mayo Clinic, intestinal obstruction secondary to carcinoma of the colon was noted in five and twenty-one cases respectively.⁶⁻⁸ A review of the pathology files at The Mount Sinai Hospital also reveals the occurrence of intestinal obstruction in a significant number of these cases.⁹ In all these cases the pseudomembranes were found proximal to the site of the intestinal narrowing. Mechanical obstruction which produces sustained elevation of the intraluminal pressure, particularly in excess of capillary pressure, has been shown to cause varying degrees of injury to the mucosa and submucosa ranging

Pseudomembranous Enterocolitis



2



3

Fig. 2. A portion of the ileum at necropsy covered by a confluent pseudomembrane. *Fig. 3.* Microscopic section of the ileum. Note the bacterial colonies on the luminal side of the pseudomembrane which has started to separate from the underlying submucosa.

from mild edema and hemorrhage to necrosis and impaired permeability.¹⁰ In addition, stasis of the intestinal contents, produced by either organic or adynamic intestinal obstruction, may upset the normal balance of the intestinal flora with further damage to the tissues. Prior to 1952, bacteriologic studies in the cases at the Mayo Clinic were inadequate, thus precluding the exact evaluation of the infectious element. Shock has also been implicated as an important etiologic factor in this frequently fatal disorder,¹¹⁻¹³ but in our patient it became clinically manifest twenty-four hours after the onset of the diarrhea and was considered to be a secondary phenomenon.

In addition to the possible causal mechanisms already mentioned, leukemia, chronic uremia, arsenic and mercury poisoning, diphtheria, and salmonella and shigella dysentery have at times been associated with pseudomembrane formation.¹⁴ This limited response of the mucosa and submucosa to a variety of offending agents suggests that acute pseudomembranous enterocolitis is a clinicopathologic syndrome with many possible inciting causes, rather than a specific disease state.

Although the jejunum, ileum, and colon are most commonly involved, the pseudomembranous lesions may occur along the entire gastrointestinal tract, extending from the esophagus to the rectum. Development of the actual membrane, composed primarily of necrotic mucosa, fibrin, cellular debris, and bacteria, is the most advanced pathologic stage and need not necessarily be present for the diagnosis to be established. An occasional patient with a fulminating clinical course has been found at necropsy to have only inflammatory or congestive alterations in the lining of the bowel.^{2, 15} An absent pseudomembrane may also be due to a spontaneous slough and has been infrequently observed in both vomitus and feces.^{16, 17} The lesion may be overlooked at necropsy if the gastrointestinal tract is not inspected carefully or is washed too vigorously.

Diagnosis

Diagnosis of acute pseudomembranous enterocolitis should always be suspected with the onset of massive diarrhea or frequent stomal discharges, with or without fever, abdominal distention and vomiting, particularly in the postoperative patient, the patient who has been receiving antibiotics, and the patient with generalized cachexia. The diagnosis has often been difficult to establish antemortem especially where other major pathology such as peritonitis or intestinal obstruction exists. Laparotomies have been erroneously performed for suspected intra-abdominal hemorrhage¹⁸ and perforation.¹⁹

Pseudomembranous Enterocolitis

Treatment

It is imperative that with the onset of massive diarrhea there be immediate fluid, electrolyte, and blood replacement. Shock often ensues within twenty-four hours and becomes irreversible unless such aggressive measures are taken. Vasopressor drugs and oxygen may be used as indicated. A stool smear and culture with sensitivity studies should be performed at once. If gram-positive cocci are found on direct smear, it is necessary to discontinue antibiotics and to substitute erythromycin, to which most staphylococci are still sensitive. Although to no avail in our patient, there has been a small but growing list of cases in which early recognition and treatment has been lifesaving.^{2, 15, 16, 17, 20} Steroid therapy has been employed with success in several patients in whom no unusual bacterial flora was found in the gastrointestinal tract.^{21, 22} Prophylaxis against pseudomembranous enterocolitis is primarily limited to the judicious use of antibiotics and the performance of repeated throat and stool cultures in patients receiving prolonged therapy.

This is the first reported case of pseudomembranous enterocolitis in association with aplastic anemia and transfusion hemosiderosis. The relationship appears to be entirely incidental, however. Despite a leukopenia in the peripheral blood, there was an excellent neutrophilic response to the infection in the small bowel. It is of interest that, contrary to the findings of a hypoplastic bone marrow on sternal aspirations during life, the marrow studied at necropsy was cellular, with erythroid depression, maturation arrest of the myeloid series, and an increase of megakaryocytes and megakaryoblasts. This is consistent with one form of aplastic anemia. The development of transfusion hemosiderosis following 200 or more transfusions is not unusual. Prior to the antibiotic era most patients did not survive long enough to receive such a vast quantity of blood.

SUMMARY

A case of acute pseudomembranous enterocolitis occurring in a non-surgical patient with aplastic anemia and transfusion hemosiderosis has been presented. Intestinal obstruction and *Staphylococcus aureus* infection of the bowel played prominent roles in the development of the lesion. A high level of suspicion for the occurrence of this disorder and the need for immediate therapy is stressed.

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EDITORIAL

Sprue in Puerto Rico

SINCE October, 1953, a research team based at the U. S. Army's Tropical Research Medical Laboratory in San Juan, Puerto Rico, has been investigating malabsorption and related problems of tropical sprue. The sprue team, established under the leadership of Capt. Frank H. Gardner, MC, was originated and sponsored by the Department of Hematology, Walter Reed Army Institute of Research. Since Captain Gardner's departure in 1955, the team has been headed by Maj. C. E. Butterworth, Jr., MC. When the project was first proposed, two rather pertinent questions were asked: (1) Why should the Army support research in tropical sprue? The possibility of such a disease's becoming a threat to the health of an American Army is remote. In fact, visitors to Puerto Rico reported that the disease had almost disappeared from the island. (2) Why should hematologists study a disease of the small intestine?

Before the team was ever established these questions and many others had been carefully considered, and the answers to them were not unreasonable. Planning for the work of the sprue team had gone on for almost a year before the team actually took the field. Colonel William S. Stone, MC, then the Commandant of the Army Medical Service Graduate School, had visited the Korean combat zone in the autumn of 1952. He was deeply impressed by the rapid loss of flesh that occurred in severely wounded battle casualties within a few days after injury. He suspected that this was not entirely a catabolic phenomenon and expressed a desire for methods to study the function of the small intestine, suspecting that malabsorption might play some part in this rapid wasting. In July, 1953, a conference was held at Walter Reed to which were invited twelve men who, for one reason or another, were interested in the relation of small-intestine function and nutrition. In his opening statement Colonel Stone expressed the reasons for the Army's interest in the study of tropical sprue as a prototype of

From the Department of Hematology, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C.

small-intestine disease whereby methods for the study of intestinal function might be developed:

The Army has run into a number of problems in the field of metabolism in which defective absorption appears to play a considerable role, not only in the acutely injured battle casualty but in many circumstances where bacterial flora alter absorption. Our understanding of the sequence of events and of the factors leading to the changes we observe is certainly very deficient. The clinical entity sprue is one of those naturally occurring phenomena in which we might be able to gain insight to the over-all problem. We propose to use the chronic disease as a mechanism to get at some of the more acute problems, such as the disturbances created by changes of bacterial flora that take place under broad-spectrum antibiotics and the extreme metabolic wasting that takes place in severely injured men and similar metabolic problems.

At this same meeting the question was brought up of how much sprue was still to be found in Puerto Rico. As things have worked out, this has never been a problem for the sprue team. Sprue is still there, perhaps not as florid as it was 20 years ago, but sprue patients "never die and never get well" and new cases appear every month. Even with a limited effort at case finding, during its first year the sprue team turned up 25 cases of small-intestine malabsorption among personnel of the United States Army stationed in Puerto Rico. Yet for many years before the advent of the sprue team a diagnosis of sprue had not been made at Rodriguez Army Hospital in San Juan.

Why were hematologists sent to study a disease of the bowel? Since the early years of this century medical practice in Puerto Rico has had a strongly hematologic flavor. In 1899 Lt. Bailey K. Ashford, a medical officer of the United States Army, was sent to Puerto Rico. His first assignment was to provide medical care for several thousand victims of a hurricane. He found that many of these Puerto Ricans had a severe anemia. Within a few weeks he had identified hookworm disease as a cause of most of the cases of anemia and, looking further, he found that hookworm was a scourge of the island. At that time 20 per cent of the deaths in Puerto Rico were due to anemia. It was largely through the phenomenal work of Dr. Ashford that this problem was brought under control. In 1904, the Porto Rico Anemia Commission was established and through this agency Dr. Ashford worked for many years. He continued his career as an Army officer and continued his service in Puerto Rico. His interest naturally broadened to many of the other health problems of the island. One of these was sprue. In

Editorial

Puerto Rico the first work done on this disease was done by Dr. Ashford and the Puerto Rican physicians whom he helped to train. The sprue that these men described was indeed characterized by intestinal symptoms but also, and almost uniformly, by a megaloblastic macrocytic anemia. In other parts of the world such an anemia may occur with sprue but the incidence is not nearly so high as in Puerto Rico. This had caused the students of sprue in other parts of the world no little concern. One of the things they were most interested to learn was whether Puerto Rican sprue was indeed the same disease that was found in India and Hong Kong. It was for these reasons that it was decided to send hematologists rather than gastroenterologists to Puerto Rico. The men who had treated sprue in Puerto Rico were hematologists, and the disease they described presented as a hematologic disease.

During its first three years the sprue team in Puerto Rico has made great progress. It has been welcomed and assisted in every way by the Puerto Rican government and the medical profession. Two physicians, Dr. Enrique Perez-Santiago and Dr. Calixto Romero-Barcelo, have been active collaborators with the sprue team. The District Hospitals operated by the Department of Health, Commonwealth of Puerto Rico, have opened their doors, and in the Bayamon District Hospital a metabolic ward has been established.

The Puerto Rican clinics continue their own important researches in tropical sprue. Dr. Ramon Suarez at the Mimiya Hospital, the dean of hematologists in Puerto Rico, studies the therapy of the disease. Dr. Angel Cintron-Rivera at the Municipal Hospital in San Juan is setting up a broad study of all megaloblastic anemias found in Puerto Rico. At the Veterans Administration Hospital at San Patricio the well-known authority, Dr. R. Rodriguez-Molina, has organized a most productive and careful investigation of fat absorption in sprue. The friendly and spontaneous cooperation among all of these groups serves to improve the efforts of each. An opportunity for the mutual exchange of detailed information has been provided by a Sprue Conference, organized each spring by Colonel David H. Naimark, MC, Commanding Officer of the Tropical Research Medical Laboratory. These week-long meetings have had as participants the sprue team, the Puerto Rican investigators, and also such interested auslanders as Drs. Chester M. Jones, Alastair C. Frazer, Perry J. Culver, Irving Grey and David A. Turner. The conferences have provided a pleasant and profitable opportunity to review each year's work and to plan the direction of investigation for the year to come.

Crosby

Sprue is a disease with readily recognizable hematologic defects such as macrocytic anemia, leukopenia, and megaloblastic bone marrow. Indeed, correction of these defects may rehabilitate the patient with sprue even though malabsorption persists. The physiology of absorption of erythrocyte-maturation factors has long been a subject of mutual interest to gastroenterologists and hematologists. In the past thirty years clarification of vitamin B₁₂-intrinsic factor relationships in pernicious anemia reflects credit on both groups. Unfortunately no such elegant definition of sprue has become manifest. In fact it remains to be seen whether intestinal malabsorption is the primary lesion or whether it is part of a generalized process. It is hoped that Army investigators using techniques developed by both gastroenterologists and hematologists may be able to shed new light on this subject of common interest to both groups. At the present time the work of the sprue team is progressing in three areas: the development of methods for the study of small-intestine function, exploration of the pathogenesis of sprue, and epidemiologic studies. In each of these areas important contributions have been made and more will be made as the work continues.

WILLIAM H. CROSBY
Lt. Col., MC, U. S. Army

Pearls of Gastroenterology

Abdomen

Abdominal Wall

Anatomic triangles

Hesselbach's: deep epigastric vessels, Poupart's ligament, lateral edge of rectus abdominis.

Grynfelt's or *Lesshaft's* (site of some lumbar hernias): bounded by twelfth rib and lower border of serratus posterior inferior above, anterior border of quadratus lumborum behind, and posterior border of internal oblique muscle in front.

Labbe's (rough area of contact between stomach and anterior abdominal wall): anterior edge of liver above, edge of false ribs on left, and horizontal line along lower border of ninth rib cartilages below.

Petit's: crest of ilium below, border of external oblique muscle anteriorly, and border of latissimus posteriorly.

¶ Xiphoid cartilage syndrome: epigastric pain or heavy feeling localized in xiphoid region, arising from malformed but unbroken xiphoid process, with tenderness on palpation. Nausea and vomiting may be produced when xiphoid is bent back. Often there is pain on deep breathing. Lying supine eases the pain (*J. A. M. A.* 154: 992, 1954).

Excerpts from a collection of gastroenterologic information compiled by Eddy D. Palmer, M. D., presently on duty with the Army abroad. Dr. Palmer is a member of the editorial board of this Journal.

AUTHOR'S NOTE: This is a potpourri of favorite information about gastroenterology. It is strictly random information, some included because it is important, some because it may easily be overlooked during the reading of the detailed standard texts, and some because it may have special meaning for gastroenterology as it is practiced during this particular era.

The references which follow some of the statements do not, by any means, indicate the sources of the statements, but rather places to look for further information.—E.D.P.

¶ Syndrome of rupture of deep epigastric vessel should be borne in mind: sudden or insidious development of a painful tender mass, usually in lower part of the abdomen. Occurs most frequently in the aged, obese, and debilitated, initiated by trauma or strain, as in cough. The pain is severe, often agonizing. Needle aspiration is futile for diagnosis or treatment because of dispersion of the blood (*J. A. M. A.* 150: 789, 1952).

¶ The umbilicus is an unusual localization for metastatic carcinoma. Usually the primary tumor lies in the kidney, biliary tract, stomach, or bowel (*J. A. M. A.* 150: 556, 1952).

Palmer

¶ Tumors of the abdominal wall are rare. Primary sarcoma, metastatic sarcoma, and metastatic carcinoma are commonest. Cysts, dermoids (Nelaton's tumor), fibromas, lipomas, hematomas, specific granulomas, and endometriomas are other possibilities (*Gastroenterology* 19: 303, 1951).

¶ Weber-Christian disease: On rare occasions "stomach pain" may be ascribed to relapsing febrile nodular nonsuppurative panniculitis of abdominal wall. Recognition of the superficial position of the pain and tenderness should be easy enough (*Am. J. M. Sci.* 225: 446, 1953).

This disease is characterized by recurring episodes of fever and by the appearance of inflammatory or necrotic nodules in the panniculus adiposus. Nodules are most fre-

quent over the abdomen, arms, legs, and breasts. Nodules are 1-3 cm. in diameter. All age groups may be affected. Females:males in 3:1 proportion. Not reported in Negroes. Regional adenopathy and splenomegaly occasionally develop.

¶ Congenital absence of the abdominal wall muscles is extremely rare. In most instances there are associated urinary retention and pyeloureterectasis. Removal of obstruction at bladder neck is usually necessary, but help for the abdominal wall must come from corseting (*Proc. Staff Meet. Mayo Clinic.* 27: 325, 1952).

¶ Hall's "electric bell" reaction: light pressure over a ventral hernia sometimes produces an immediate belch.



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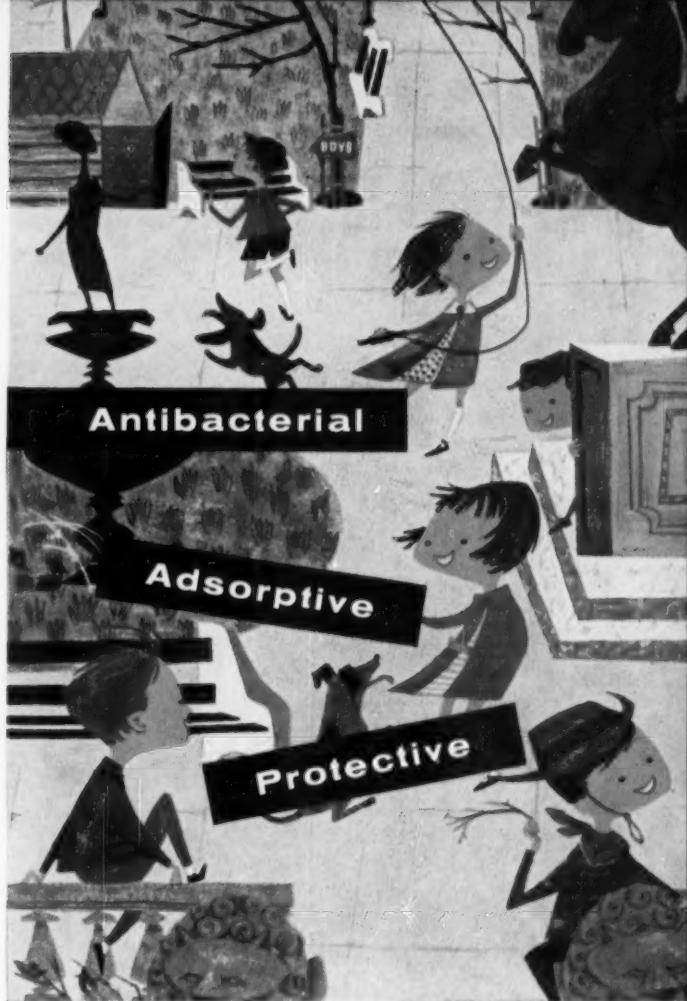
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